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**Title**

Oncologic outcome after local recurrence of chondrosarcoma: analysis of prognostic factors

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**Abstract**

*Background:* Because of the limited effects of radiation therapy and chemotherapy, surgery remains the primary treatment modality for local control of chondrosarcoma either for primary or locally recurrent cases. Surgical treatment of locally recurrent chondrosarcoma is especially challenging because of the altered anatomy and scarring from the previous surgery, which may result not only in the compromise of the surgical margin but also in significant morbidity of the patient.

In general, the development of local recurrence (LR) is thought to be associated with increased rate of metastasis and worse survival in chondrosarcoma. However, literature on outcome after LR in chondrosarcoma is scarce with the reported wide range of survival rate from 17% to 76% at 10 to 20 years. Moreover, better identification of prognostic factors is needed to guide decisions regarding treatment and surveillance in locally recurrent chondrosarcoma.

*Questions/Purposes:* This study was undertaken in a series of locally recurrent chondrosarcomas treated in a single institution, 1) to evaluate post-LR oncologic outcomes of disease-specific survival and subsequent LR and 2) to identify prognostic factors for post-LR oncologic outcomes.

*Patients and Methods:* From the prospectively collected database of our institute, 150 consecutive patients who had undergone surgery for chondrosarcoma of extremities or pelvis were reviewed. Among these 150 patients, we identified 40 (26%) patients with LR. Thirty-seven of these 40 patients underwent surgery, and 5 patients with a follow-up duration shorter than 1 year after LR and 4 patients with low grade chondrosarcoma of the extremities were excluded, which left 28 patients for analysis. The mean follow-up duration of all patients was 8.4±7.5 years (range, 1.2~31.0). The mean follow up duration of survivors was 11.1 years (range, 3.0 ~31.0).

Medical records were reviewed for the potential clinic-pathologic variables that might influence post-LR oncologic outcome in chondrosarcoma: (1) patient demographics, (2) factors related to the primary tumor, (3) pattern of LR, and (4) treatment of LR.

Anatomical site was classified as appendicular skeleton (n=10) or axial skeleton (18). Histological types were comprised of conventional (n=17), clear cell (3), dedifferentiated (3), myxoid (2), secondary (2), and mesenchymal (1). There were 1 grade 1, 17 grade 2 and 9 grade 3 tumors. All primary tumors were resected with wide margins in 19 cases, marginal in 5 cases and intralesional curettage in 4 cases.

As for patterns of LR, LR-free interval (LRFI) was recorded as the time from resection of the primary tumor until the development of LR. The median LRFI was 1.6 years (range, 0.4-15.0). Mean number of local recurrences was 1.3 (range, 1-4) and 7 patients had more than one episode of local recurrence. Three patients had metastatic disease at the time of diagnosis of LR.

Regarding the treatment of LR, surgical margin, pathological margin, the administration of radiation therapy and chemotherapy were investigated. Surgical margins were wide (n=11), marginal (3) or intralesional (4). Four patients with intralesional margin had axial tumors that were surgical unresectable and underwent piecemeal resection. Histological margins were negative in 21 cases and positive in 7. Postoperative radiotherapy was provided as adjuvant treatment in 4 patients when surgical margins were considered inadequate. Chemotherapy was given in 3 patients with systemic disease.

*Results:* Among the 28 patients, 18 patients were alive and 10 patients died of disease during the follow-up. The post-LR survival rate was  $58.6 \pm 10.3\%$  at 5 years at 10 years (Fig. 1). Univariate analysis revealed age  $\geq 50$  years at LR ( $p=0.011$ ), gender ( $p=0.045$ ), and LRFI  $< 1$  year ( $p=0.011$ ) as prognosticators of poor post-LR survival (Table 1). In multivariate analysis using the Cox proportional hazards model, two variables remained significant: age  $\geq 50$  years at LR (HR=5.95,  $p=0.011$ ) and LRFI  $< 1$  year (HR=4.8,  $p=0.011$ )

In all, 7 patients had subsequent LR. The mean time to subsequent LR was 2.7 years (range 0.5-7.5). The 5- and 10-year subsequent LR-free survival rates were  $68.1 \pm 11.4\%$  and  $51.1 \pm 17.1\%$  respectively. Univariate analysis of variables showed that marginal or intralesional surgical margins for LR surgery had higher risk of subsequent LR ( $p=0.022$ ) and remained as an independent variable in multivariate analysis (HR=5.01, CI 95%=1.09~22.98,  $p=0.038$ ).

*Conclusions:* Long term survival of locally recurrent chondrosarcoma is achievable in a substantial number of

patients. Older age at onset of LR and shorter interval from primary surgery to local recurrence identifies high risk patients for poor post-LR survival while wide surgical margins at LR surgery reduces the risk of subsequent LR.

Figure 1. Kaplan-Meier analysis curve for post-local recurrence survival shows survival rates of  $58.6 \pm 10.3\%$  at 5 years, which plateaus until 25 years. LR: local recurrence

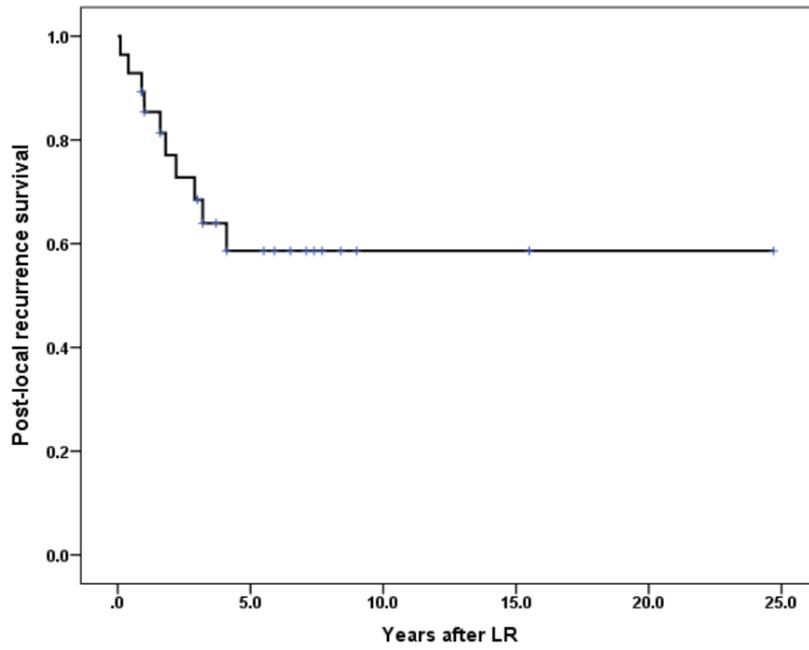


Table 1. Factors associated with post-LR survival

Factor	Univariate		Multivariate		
	5y disease-specific survival	P	HR	95% CI	P
<b>Age</b>		0.008			0.011
< 50y (18)	72.3±11.9		1		
≥ 50y (10)	35.0±16.0		5.95	1.49~23.7	
<b>Gender</b>		0.045			
Male (20)	73.1±10.3				
Female (8)	18.8±16.7				
<b>Location</b>		0.274			
Appendicular (10)	78.8±13.4				
Axial (18)	47.0±13.5				
<b>Histological grade</b>		0.458			
Low grade (1)	100±0.0				
High grade (27)	56.7±10.6				
<b>LR-free interval</b>		0.008			0.011
≥ 1y (21)	78.8±9.5		1		
< 1y (7)	14.3±13.2		4.76	1.34~16.95	
<b>Surgical margin at LR surgery</b>		0.598			
Wide (21)	53.5±12.3				
Marginal or Intralesional (7)	71.4±17.1				
<b>Post-LR radiation</b>		0.941			
No radiotherapy (24)	59.1±10.6				
Radiotherapy (4)	50.0±35.4				
<b>Metastasis before LR</b>		0.273			
Absent (25)	62.3±10.9				
Present (3)	33.3±27.2				

HR, hazard ratio; CI, confidence interval; LR, local recurrence